REMARKS

Claims 2-20, 24, 26-28, 31, 46, 48-53 and 55 are pending. Claims 14-18, and 55 have been withdrawn as directed to non-elected subject matter there being no allowable generic or linking claim at this time. Claims 21-23, 25, 29-30, 32-45, 47 and 54 have been canceled without prejudice. Upon entry of this amendment claims 2-13, 19, 20, 24, 26-28, 31, 46, and 48-53 are subject to examination. Claims 2, 5, and 7 have been amended. Claim 2 has been amended to recite a particular length of the dsRNA and that the dsRNA is naked. Additionally, claim 2 has been amended to recite that the method is done with intent. Claim 5 has been amended to correct a typographical error. Claim 7 has been amended to correct a grammatical error. These amendments find support in the specification and the previously submitted claims; thus, no new matter is presented. Each of the objected and rejected set forth in the Office Action are addressed below in the order presented therein

Priority

Applicants acknowledge Examiner's statement that the effective priority date of the instant application is granted as April 18, 2002. The Office, however, inadvertently misstated the filing date of the PCT application. The Office stated that PCT/EP03/04002 was filed April 18, 2002. (Final Office Action, page 2). The filing date of PCT/EP03/04002 is April 16, 2003. All other dates used by the Office appear to be correct.

The Office acknowledges Applicants' claim for foreign priority under 35 U.S.C. §119(a)-(d) and notes that while a certified copy of foreign patent application EP02008671.5, filed April 18, 2002, has been filed in the instant application, a certified English translation has not been provided. Applicants note that pursuant to MPEP Appendix R Patent Rules §1.55(a)(4)(i)(C), an English translation of a non-English language foreign application is not required except when specifically required by the Examiner. Applicants respectfully request clarification as to whether the Examiner specifically requires a certified English translation of the foreign priority document. If such translation is required by the Examiner, Applicants will attend to the matter.

Objections

Claims 5 and 7 stand objected to due to a typographical and grammatical error, respectively. Claims 5 and 7 have been amended in accordance with the Examiner's suggestion. In view of the amendments to claims 5 and 7, Applicants respectfully request that the objection be withdrawn.

Rejections under 35 U.S.C. § 112

Enablement

Claims 5-6 and 50-53 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office alleges that the claims are not enabled to "increase the expression of a gene in a cell in the eye." Applicants respectfully disagree that the claims are not enabled because the Office has misinterpreted the claim.

Claims 5 and 6 are dependent upon claim 2, and recite that the "dsRNA ***inhibits*** expression of a target gene that is expressed behind the blood-brain or blood-retina barrier" and where the target gene encodes a cellular mRNA, respectively. (emphasis added) Claims 5 and 6 were amended in Applicants' response filed July 24, 2008. The amendment to claim 5 recites that the expression of the target gene is inhibited, not expressed. As acknowledged by the Office, the specification enables one of skill in the art to inhibit expression. (See, Office Action, page 7). Accordingly, the claims are enabled because one of skill in the art would be able to inhibit the target gene expression without undue experimentation. "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." (M.P.E.P. §2164.04, citing *In re Wright*, 999 F.2d 1557, 1562, (Fed. Cir. 1993)). The Examiner has failed to establish a reasonable basis to question the enablement provided for the pending claims.

Claims 50-53 are directed to other embodiments wherein the inhibition of target gene expression treats a retinal or a degenerative retinal disease. The Office alleges that to treat a retinal or degenerative retinal disease would require undue experimentation. Applicants respectfully disagree.

The Examiner notes that the present application discloses working examples that disclose that "systemic administration by tail vein injection or local administration by retrobulbar injection . . . of naked dsRNA" is able to inhibit expression of a target gene that is expressed behind the blood-brain or blood-retina barrier (Final Office Action, page 6). The Office does not question the enablement of these working examples. Rather the Office alleges that Experimental Procedures 2-5 do not disclose "the optimal time of efficacy of post-transcriptional silencing" or the optimal dsRNA concentration for post-transcriptional gene silencing. (Final Office Action, page 6). However, these allegations, whether true or not, are not elements of the claim and are not sufficient to question the enablement of the claim. Based upon these teachings one of skill in the art would not require undue experimentation to practice the claimed invention.

Applicants describe and teach how to deliver a dsRNA molecule across the blood-brain and/or blood-retina barrier. The method of delivery is sufficient to enable the pending claims. One of skill in the art would only need to use routine experimentation to pick a specific target gene and treat a retinal or a degenerative retinal disease in light of the teachings of the specification. The Office suggests that the present invention "falls within the realm of gene therapy." The present method is not related to gene therapy. The Office sites the Deonarain reference (Expert Opin. Ther. Pat. 8:53-69, 1998) to suggest the claims are not enabled. The Deonarian reference shows that the present invention is not related to gene therapy. Deonarain states that the intended result of gene therapy is to express the target gene at adequate levels for a long enough period of time. (Office Action, p.10). In contrast, the present invention is directed to inhibiting expression. Therefore, the alleged problems with gene therapy are irrelevant as to whether the pending claims are enabled. The other references cited by the Office all relate to sustained expression of a protein. If the Office maintains the present rejection that the claims are not enabled using the comparison of gene therapy, Applicants respectfully request that the Office further explain why two dramatically different techniques are being compared.

The Office's own argument regarding "the efficacy of antisense-based therapies" is evidence that the Office is not establishing a reasonable basis to question the enablement of the pending claims because the pending claims are not directed to antisense-based therapies. Although the intended result of inhibiting expression may be similar when comparing antisense

and dsRNA techniques, the mechanisms and methodologies are distinct. The difference between the mechanisms and methodologies means that the Office's allegation about one therapy cannot be applied to a different therapy to establish a reasonable basis to question the enablement of the pending claims. There is no rational reason why the alleged unpredictability of one technique can be applied to a different technique that works, as acknowledged by the Office, by a different mechanism. Therefore, the Office has failed to meet its burden to challenge the enablement of the claims.

The Office also alleges that "it appears that all of the developments in nucleic-acid based therapies have not been sufficient to overcome this one basic obstacle—drug delivery" and that delivery is unpredictable. The claims are not directed to all nucleic acid based therapies. Rather, the claims are directed to a method that uses one or more double-stranded oligoribonucleotides. Additionally, Applicants have demonstrated that they have overcome any alleged obstacle for delivery of dsRNAs to the cells or tissues of the eye, which appears to be the basis of the Examiner's enablement rejection. Applicants have demonstrated that dsRNA can be trafficked across the blood-brain or blood-retina barrier (See Examples 2-5). The references cited by the Office have failed to establish a reasonable basis to challenge this fact. Therefore, the Office's allegation that the biggest obstacle to enabling the method is that delivery may not work has been overcome by the present application.

Accordingly, the claims are enabled because one of skill in the art using only the specification and, at most, routine experimentation would be able to practice the claimed invention. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 2, 7, 13, 21-22, 24-28, 31, and 54 are rejected under 35 U.S.C §102(b), in light of Carter (U.S. Patent No. 5,712,257). Applicants note that the claims are now amended to recite a method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier to an organism in need thereof comprising introducing a composition comprising one or more naked double-stranded oligoribonucleotides (dsRNA) consisting of 21 to 23 nucleotides into a cell,

tissue or organism outside the blood-brain or blood-retina barriers, wherein said dsRNA is trafficked across said blood-brain or blood-retina barrier. In order for a reference to anticipate a claim, the reference must disclose each and every element as arranged in the claim. The claims are not anticipated because Carter fails to teach each and every element of the claim.

Carter states that a "key to the present invention is the building of a micelle on or around the dsRNA" (Carter, Column 3, lines 64-65). This key feature of Carter would not include naked dsRNA. Additionally, the Carter reference states that "naked dsRNA has a high negative charge and may be physically repulsed by the cell." Accordingly, the Carter reference fails to teach the introduction of naked dsRNA as recited in the pending claims. Additionally, the Carter reference fails to disclose a method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier to an organism in need thereof. As discussed previously, the Carter reference fails to disclose or suggest that it would be possible to traffic a dsRNA across the blood-brain or blood-retina barrier. The amendment to the claim that recites "in need thereof" requires that the person performing the method recognize the need to traffic the dsRNA molecule across the blood-brain or blood-retina barrier. Since the Carter reference fails to have any recognition or intent to traffic a dsRNA molecule across the blood-brain barrier, the Carter reference also fails to teach this element. Therefore, the Carter reference fails to anticipate the claims because it fails to teach each and every element of the claims. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §102 be withdrawn.

Claims 2-3, 5-10, 13, 19-22, 24, 26-28, 31, and 50-54 are rejected under 35 USC § 102(a) and 35 U.S.C. § 102(e), in light of LeFleur et al. (U.S. Patent No. 6,433,145). Applicants note that the claims are now amended to recite method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier to an organism in need thereof comprising introducing a composition comprising one or more naked double-stranded oligoribonucleotides (dsRNA) consisting of 21 to 23 nucleotides into a cell, tissue or organism outside the blood-brain or blood-retina barriers, wherein said dsRNA is trafficked across said blood-brain or blood-retina barrier. For a reference to anticipate a claim the reference must disclose each and every element as arranged in the claim. The LeFleur reference fails to disclose a dsRNA that is 21 to 23 nucleotides. Therefore, the claims are not anticipated because the LeFleur fails to teach each and every

element of the claim. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §102 be withdrawn.

Claims 2-13, 21-22, 24, 26-28, 31, 46, 50 and 54 are rejected under 35 U.S.C. §102(a) and 35 U.S.C. §102(e), in light of King (U.S. Patent Application No. 2002/0165158). Applicants note that the claims are now amended to recite method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier to an organism in need thereof comprising introducing a composition comprising one or more naked double-stranded oligoribonucleotides (dsRNA) consisting of 21 to 23 nucleotides into a cell, tissue or organism outside the blood-brain or blood-retina barriers, wherein said dsRNA is trafficked across said blood-brain or blood-retina barrier. For a reference to anticipate a claim the reference must disclose each and every element as arranged in the claim. The King reference fails to disclose a method for delivery to an organism in thereof comprising a naked dsRNA consisting of 21 to 23 nucleotides. Therefore, the claims are not anticipated because the King reference fails to teach each and every element of the claim. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §102 be withdrawn.

Claims 2, 5-10, 13, 19-22, 24, 26-28, 31, and 48-54 are rejected under 35 USC § 102(e), in light of Tolentino et al. (U.S. Patent No. 7,148,342). Applicants hereby explicitly retract the following statement made in the previously filed response, which was filed on July 24, 2008 in response to the Office Action mailed January 24, 2008:

> Tolentino et al. fails to teach how to deliver dsRNA across the blood-brain or the blood-retina barrier. Moreover, there is no indication that dsRNA can even cross the blood-brain or the blood-retina barrier. The additional references to other elements of the claims merely recite added elements, without addressing this primary deficiency. As such, Tolentino et al. does not teach or even suggest each and every element of the claims.

(Applicants Response, p. 11, filed July 24, 2008). Applicants reserve the right to argue to the contrary to what was stated in the response filed July 24, 2008 at any future opportunity.

Applicants now point out that the Tolentino reference is not prior art. As acknowledged by the Examiner, the priority date of the present application is April 18, 2002. The Tolentino

reference claims priority to a provisional application that was filed July 24, 2002. Accordingly, the Tolentino reference is not prior art against the present application.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §102 be withdrawn. Thus, withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 103

Claims 2-13, 19-22, 24, 26--28, 31, 46, and 48-54 are rejected under 35 U.S.C. §103(a), in light of Robinson et al. (U.S. Patent No. 5,814,620) in view of LeFleur et al. (U.S. Patent No. 6,433,145), and Tuschl et al. (U.S. Patent Application No. 2002/0086356). The Office alleges that the claims are obvious because "it would have been obvious . . . to substitute an antisense gene-silencing RNA . . . with a double stranded gene-silencing RNA . . . with a reasonable ***chance*** of success because the simple substitution of one known element for another would have yield predictable results" (Final Office Action, p. 24, emphasis added). The Office alleges that "one of ordinary skill in the art recognized that . . . siRNAs and antisense oligonucleotides can be used to produce the same effect." The Office alleges that siRNAs and antisense oligonucleotides are art-recognized equivalents that may be used for the same purpose (Office Action p. 25). Applicants respectfully disagree.

The claims are not obvious because the Office has not provided a sufficient, articulated reason as to why the claims are obvious. "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." The Office alleges that siRNA and antisense are equivalents. The Office, however, has failed to provide a single reference showing that antisense and siRNA are equivalents. For example, the Office states that both siRNA and antisense inhibit gene expression. However, the fact that two different classes of compounds inhibit gene expression does not make the compositions equivalents. As acknowledged by the Office, siRNA and antisense work by "***different*** biochemical mechanisms " (Office Action, p. 24, emphasis added) The fact that the compositions work by "different"

mechanisms indicates that antisense and dsRNA are ***not*** equivalents. Therefore, the present invention is not a mere substitution and, thus, the Office has failed to make a proper *prima facie* obviousness rejection.

Additionally, the Office has failed to provide a reference or a combination of references showing that antisense and dsRNA can be substituted for one another without any changes and provide a reasonable expectation of success. The present application states that prior to the present invention, "the blood-brain barrier [and] the blood-retina barrier . . . represent[] a physiological barrier for the uptake of medication by the inner part of the eye, and makes pharmacological therapy of ocular diseases very difficult." Therefore, prior to the present invention one of skill in the art would not have had a reasonable expectation of success that it would have been possible to traffic a dsRNA composition across the blood-brain or blood-retina barrier because it has been stated that it was "very difficult." Conclusory statements by the Office that there would have been a reasonable expectation of success without pointing out why there would have been a reasonable expectation of success are insufficient.

The Office has also not demonstrated that someone intending to traffic naked dsRNA across the blood-brain or blood-retina barrier would have had a reasonable expectation of success. The references cited by the Office fail to disclose this combination. Even if the references did yield the combination, the references fail to create a reasonable expectation of success for one of skill in the art. As discussed previously, there is no indication that dsRNA can even cross the blood-brain or the blood-retina barrier. The additional references to other elements of the claims merely recite added elements, without addressing this primary deficiency. As such, the reference do not teach or even suggest each and every element of the claims with a reasonable expectation of success. Thus, withdrawal of the rejection is respectfully requested.

CONCLUSION

For the reasons discussed above, Applicant respectfully requests reconsideration of the rejections of the claims. Applicant believes that these claims are in proper form for allowance. If the undersigned can be of assistance to the Examiner regarding any of the above, please contact the undersigned at the number set forth below.

It is not believed that any additional fees are due; however, in the event that an additional fee is required for this response, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-0436.

Respectfully submitted,

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